

Initial REMS Approval: 08/OCT/2013

Most Recent Modification: 04/DEC/2015

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Adempas[®] (riociguat tablets)

Bayer HealthCare Pharmaceuticals

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Risk Evaluation and Mitigation Strategy (REMS)

I. GOALS

The goals of the Adempas REMS are:

1. To inform prescribers, patients, and pharmacists about the serious risk of teratogenicity and safe-use conditions for Adempas
2. To minimize the risk of fetal exposure and adverse fetal outcomes in Females of Reproductive Potential (FRP) prescribed Adempas:
 - a. Females who are pregnant must not be prescribed Adempas
 - b. Females taking Adempas must not become pregnant

II. REMS ELEMENTS

A. Medication Guide

A Medication Guide will be dispensed with each Adempas prescription in accordance with 21 CFR 208.24.

The *Adempas Medication Guide* is part of the REMS and is appended.

B. Elements to Assure Safe Use

1. **Healthcare providers (HCPs) who prescribe Adempas will be specially certified.**
 - a. Bayer will ensure that HCPs who prescribe Adempas are specially certified. Bayer will ensure that to become certified, HCPs agree on the *Adempas REMS Prescriber Enrollment and Agreement Form* to:

- i. Read the *Prescribing Information (PI)*, the *Adempas Medication Guide*, and the *Prescriber and Pharmacy Guide for the Adempas REMS Program*
- ii. Enroll all females in the Adempas REMS Program by completing the designated sections of the *Adempas Patient Enrollment and Consent Form*
- iii. Determine whether each female is of reproductive potential as defined in the *Prescriber and Pharmacy Guide for the Adempas REMS Program*
- iv. Advise all females that Adempas is only available through a restricted distribution program called the Adempas REMS Program
- v. For FRP (as defined by *Prescriber and Pharmacy Guide for the Adempas REMS Program*):
 1. Review the *Adempas Medication Guide* and the *Adempas REMS Program Guide for Females Who Can Get Pregnant* with the patient prior to initiating treatment
 2. Counsel FRPs about the risk of teratogenicity, the need to use reliable contraception as defined in the *Prescriber Guide for the Adempas REMS Program* during Adempas treatment and for one month following treatment discontinuation, and her medical options in the event of unprotected sexual intercourse or known or suspected contraception failure.
 3. Order and review a pregnancy test prior to initiation of Adempas treatment, monthly during treatment, and for one month following treatment discontinuation
 4. Counsel the FRP if she is not complying with the required testing or if she is not using appropriate contraception as specified for FRP
 5. Counsel FRP to immediately contact her healthcare provider if she misses a menstrual period or suspects that she is pregnant
 6. Report any changes or misclassification in reproductive status by completing the *Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form* within ten (10) business days of becoming aware of the change
- vi. For Pre-Pubertal Females of Non-Reproductive Potential (FNRP) (as defined by the *Prescriber and Pharmacy Guide for the Adempas REMS Program*):
 1. Counsel the Pre-pubertal female and/or a parent/guardian about the risk of teratogenicity

2. Review the *Adempas Medication Guide* with the patient and/or a parent/guardian
 3. Counsel the pre-pubertal female and/or a parent/guardian to immediately contact her healthcare provider if she begins to menstruate
 4. Evaluate pre-pubertal females age 8 or older at least annually for any change in reproductive status and complete the *Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form*.
 5. Report any change or misclassification in reproductive status by completing the *Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form* within 10 business days of becoming aware of the change
- vii. For Post-Menopausal FNRP (as defined by the *Prescriber and Pharmacy Guide for the Adempas REMS Program*):
1. Report any change or misclassification in reproductive status by completing the *Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form* within 10 business days of becoming aware of the change
- viii. Females with other medical reason for permanent, irreversible infertility (as defined by the *Prescriber and Pharmacy Guide for the Adempas REMS Program*):
1. Report any change or misclassification in reproductive status by completing the *Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form* within 10 business days of becoming aware of the change
- ix. Report any pregnancy during Adempas treatment to Bayer with all available information.

b. Bayer will:

- i. Ensure that prescribers' enrollment information and date of agreement are linked to their enrolled patients' information in a validated secure database
- ii. For all females, ensure that the patient information from a new prescriber is linked in the Adempas REMS Program database with certification information from the prior prescriber when a patient changes prescribers
- iii. Maintain a validated secure database of certified prescribers in the Adempas REMS Program. Bayer will ensure that prescribers' REMS

requirements are met and may de-enroll noncompliant prescribers until the requirements are met

- iv. The revised *Adempas REMS Program Website* will be available within 60 days after REMS modification approval. All materials listed in or appended to the Adempas REMS Program will be available through the Adempas REMS Program Website (www.adempasREMS.com) or by calling the Adempas REMS Program Coordinating Center at 1-855-423-3672.
- c. The following materials are part of the Adempas REMS Program and are appended:
 - *Adempas REMS Prescriber Enrollment and Agreement Form*
 - *Prescriber and Pharmacy Guide for the Adempas REMS Program*
 - *Adempas REMS Guide for Females Who Can Get Pregnant*
 - *Adempas Patient Enrollment and Consent Form*
 - *Adempas REMS Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form*
 - *Adempas REMS Program Website* (www.adempasREMS.com)
 - *Adempas Patient Enrollment and Consent Form for the Veterans Administration (V.A.)*

2. Pharmacies that dispense Adempas will be specially certified.

Outpatient Dispensing

- a. Bayer will ensure that pharmacies that dispense Adempas are specially certified. Bayer will ensure that to be certified, pharmacies that dispense Adempas have an authorized representative who is trained on the Adempas REMS Program and who attests that they will:
 - i. Train all dispensing staff on the Adempas REMS Program procedures and REMS materials prior to dispensing Adempas
 - ii. Establish processes and procedures to ensure the following REMS requirements are met
 - 1. Verify that the patient's prescriber is enrolled in the Adempas REMS Program
 - 2. Verify that females are enrolled in the Adempas REMS Program prior to dispensing each prescription of Adempas

3. Dispense Adempas only to patients who have a prescription written by an enrolled prescriber in the Adempas REMS Program
4. Dispense Adempas only to females who are enrolled in the Adempas REMS Program and have a prescription written by an enrolled prescriber in the Adempas REMS Program
5. Receive and accept a Patient Enrollment and Consent Form only from the Adempas REMS Program Coordinating Center
6. Verify reproductive status of all females with information provided by the REMS Coordinating Center prior to dispensing each prescription of Adempas
7. Not transfer Adempas to any pharmacy, practitioner, or healthcare setting not certified by the Adempas REMS program.
8. Only dispense up to a 30-day supply of Adempas to FRPs
9. For FRP (as defined in the *Prescriber and Pharmacy Guide for the Adempas REMS Program*):

1. Counsel FRP on the risk of serious birth defects and the need to use reliable contraception (as defined in the *Prescriber and Pharmacy Guide to the Adempas REMS Program*) during Adempas treatment and for one month after stopping Adempas treatment

- I. Inform FRP of the requirement to complete a pregnancy test every month and to inform her prescriber immediately if she misses a menstrual period or suspects that she may be pregnant

- II. Dispense up to a 30-day supply of Adempas to FRP only upon completing the following process:

- a) Obtain confirmation from FRP that the pregnancy testing was completed
- b) If unable to obtain confirmation from FRP that the pregnancy testing was completed, or if the FRP cannot be reached, obtain confirmation from the patient's prescriber

- a. If the prescriber for the FRP cannot confirm that the pregnancy testing was completed, the certified outpatient pharmacy must remind the

- prescriber of his or her obligation to order and review monthly pregnancy tests
 - b. Ask the prescriber whether he or she authorizes the refill of Adempas. The FRP is eligible to receive a 30-day supply of Adempas only if the prescriber authorizes the refill
- iii. Notify Bayer of any reports of pregnancy
- iv. Provide dispensing data for all enrolled patients to the Adempas REMS Program
- v. Agree that they may be audited by the FDA, Bayer, or a third party designated by Bayer
- b. Bayer will ensure the Adempas REMS Program Coordinating Center notifies certified pharmacies of a patient's change or misclassification in reproductive status within one business day of receipt of a completed *Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form*

Inpatient Dispensing

- a. Bayer will ensure that only inpatient pharmacies (including, but not limited to, inpatient pharmacies in hospitals, long-term care facilities, prisons) that are certified in the Adempas REMS Program may stock Adempas for patients being treated in the inpatient setting. In order to become certified in the Adempas REMS Program, an authorized representative must complete and submit an *Adempas REMS Program Inpatient Pharmacy Enrollment Form*, agreeing to:
 - i. Complete training in the Adempas REMS Program by reading the *Adempas Prescribing Information*, *Adempas Medication Guide* and the *Prescriber and Pharmacy Guide for the Adempas REMS Program*
 - ii. Train all dispensing staff on the Adempas REMS Program requirements and Adempas REMS materials prior to dispensing Adempas.
 - iii. Establish processes and procedures to ensure the following REMS requirements are met
 - 1. Dispense only after contacting the Adempas REMS Program Coordinating Center to confirm the inpatient is under the care of a HCP certified in the Adempas REMS program
 - 2. Adempas will only be dispensed to inpatients who are already enrolled in the Adempas REMS Program or who will be enrolled prior to discharge from the hospital.

3. Not transfer Adempas to any pharmacy, practitioner, or healthcare setting not certified by the Adempas REMS program
4. Dispense no more than a 15-day temporary supply of Adempas to any patient upon discharge from the healthcare facility
- iv. Audits by the FDA, Bayer, or third party designated by Bayer
- v. Notify Bayer of reports of pregnancy during Adempas treatment and provide all available treatment information
- vi. Develop a process to track compliance with the conditions above and provide information about its compliance to Bayer upon request
- b. Bayer will ensure that if an inpatient pharmacy needs Adempas and is not enrolled in the Adempas REMS Program, the inpatient pharmacy can contact the Adempas REMS Program Coordinating Center for assistance in obtaining up to a 15-day supply of Adempas for a specific inpatient while initiating enrollment.
- c. The following materials are part of the REMS and are appended:
 - *Prescriber and Pharmacy Guide for the Adempas REMS Program*
 - *Adempas REMS Program Inpatient Pharmacy Enrollment Form*

3. Adempas will be dispensed to females with evidence or other documentation of safe-use conditions

- a. Bayer will ensure that to become enrolled, or when changing prescribers, each female must complete the designated sections of the *Adempas Patient Enrollment and Consent Form*.
- b. By completing the *Adempas Patient Enrollment and Consent Form* each FRP acknowledges that she has:
 - i. Been counseled on the risks of Adempas, including the risk of serious birth defects
 - ii. Read the *Adempas Medication Guide* and the *Adempas REMS Program Guide for Females Who Can Get Pregnant*
 - iii. Agreed to be contacted prior to each dispensing of Adempas to obtain confirmation that pregnancy testing was completed
 - iv. Agreed to be counseled each month by the pharmacy on the need to use reliable contraception during Adempas treatment and for one month after stopping Adempas treatment
 - v. Agreed to have a pregnancy test every month during Adempas treatment and for one month after stopping Adempas

- vi. Agreed to immediately notify her healthcare provider if she misses a menstrual period or suspects that she is pregnant
- vii. Agreed to be contacted by Bayer if she becomes pregnant while on Adempas or within one month after stopping Adempas

C. Implementation System

The Implementation System will include the following:

- a. Bayer will maintain a validated secure database of enrolled prescribers, certified pharmacies, enrolled females, and Adempas dispensing data from certified pharmacies to monitor and evaluate implementation of the elements provided for under Sections B.2. and B.3 above.
- b. Bayer will monitor the distribution of Adempas to ensure that the drug is only shipped to certified pharmacies.
- c. Bayer will track Adempas dispensing data and monitor certified pharmacies to ensure compliance with the Adempas REMS Program and institute corrective actions if they are non-compliant.
- d. Bayer will ensure an authorized representative of each certified pharmacy is trained on the REMS program and trains staff appropriately.
- e. Bayer will monitor and evaluate the implementation of the elements provided for under Sections B.B.2 and B.0 above and take steps to work to improve implementation of these elements if needed.
- f. Bayer will maintain an Adempas REMS Program Coordinating Center to support patients, prescribers, certified pharmacies, and distributors in interfacing with the Adempas REMS Program.
- g. Bayer will audit all certified outpatient pharmacies, distributors, and the Adempas REMS Coordinating Center within 180 days after they are certified in the Adempas REMS program to ensure the Adempas REMS Program is implemented as directed. Thereafter, Bayer will include the certified outpatient pharmacies, all distributors and the Adempas REMS Coordinating Center in the company's annual audit plan. At least 10% of certified inpatient pharmacies that have ordered Adempas will be audited each year. Corrective actions will be instituted if noncompliance is found.
- h. Bayer will ensure that all materials listed in or appended to the Adempas REMS Program will be available through the Adempas REMS Program Website (www.adempasREMS.com) or by calling the Adempas REMS Program Coordinating Center at 1-855-423-3672.

D. Timetable for Submission of Assessments

Bayer will submit REMS Assessments to FDA 6 months and 12 months from the date of initial approval of the REMS, and annually thereafter. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Bayer will submit each assessment so that it will be received by the FDA on or before the due date.